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Netherlands Twin Register: From Twins to Twin Families

Dorret I. Boomsma, Eco J. C. de Geus, Jacqueline M. Vink, Janine H. Stubbe, Marijn A. Distel, Jouke-Jan Hottenga, Danielle Posthuma, Toos C. E. M. van Beijsterveldt, James J. Hudziak, Meike Bartels, and Gonneke Willemsen

Department of Biological Psychology, Vrije Universiteit, Amsterdam, the Netherlands

In the late 1980s The Netherlands Twin Register (NTR) was established by recruiting young twins and multiples at birth and by approaching adolescent and young adult twins through city councils. The Adult NTR (ANTR) includes twins, their parents, siblings, spouses and their adult offspring. The number of participants in the ANTR who take part in survey and / or laboratory studies is over 22,000 subjects. A special group of participants consists of sisters who are mothers of twins. In the Young NTR (YNTR), data on more than 50,000 young twins have been collected. Currently we are extending the YNTR by including siblings of twins. Participants in YNTR and ANTR have been phenotyped every 2 to 3 years in longitudinal survey studies, since 1986 and 1991 for the YNTR and ANTR, respectively. The resulting large population-based datasets are used for genetic epidemiological studies and also, for example, to advance phenotyping through the development of new syndrome scales based on existing items from other inventories. New research developments further include brain imaging studies in selected and unselected groups, clinical assessment of psychopathology through interviews, and cross-referencing the NTR database to other national databases. A large biobank enterprise is ongoing in the ANTR in which blood and urine samples are collected for genotyping, expression analysis, and metabolomics studies. In this paper we give an update on the YNTR and ANTR phenotyping and on the ongoing ANTR biobank studies.

The Netherlands Twin Register (NTR) consists of two groups of twins and twin families who have participated in research projects since the 1980s. Young twins (YNTR) are registered at birth by their parents, who are approached through 'birth felicitation' services. Adolescent and young adult twins (ANTR) were recruited through city councils in 1990 and1991, and through additional efforts in later years. Demographic characteristics, recruitment and data collection procedures in these samples are described in detail elsewhere (Bartels et al., in press; Boomsma et al., 2000, 2002; Koopmans et al., 1999; Rietveld et al., 2000; Stubbe et al., 2005: Vink et al., 2004). In this paper we give an update on the ANTR and YNTR and describe some new developments in phenotyping and biobank studies.

ANTR

Table 1 offers a summary of the number of family members registered with the ANTR who participated at least once in one of the surveys or in one of the laboratory studies. Families of adolescent and adult twins have been extended to include parents, siblings, spouses and offspring (over 18 years) of the twins and siblings. The total of nearly 22,000 participants in the survey studies comes from 5546 families (some families are linked) and includes 4536 families with a complete twin pair, 761 families with an incomplete pair (i.e., only one twin participates) and 249 families in which the twins did not participate but their family members did. In Figure 1, information on the number of twins as a function of birth cohort and zygosity-by-sex groups is given. The majority of the twins are young adults (average age on January 1, 2007 is 35.5 years; SD = 10.0). The largest group of twins is formed by monozygotic (MZ) females (29%), directly followed by dizygotic (DZ) twins from opposite-sex pairs (25%). Overall, slightly fewer men (45%) then women (55%) take part. For the twins, the sex distribution of men and women is 40% men and 60% women, for their siblings it is 45% and 55%, and for their parents 47% and 53%. For the spouses, a reversed pattern is seen: there are 64% male and 36% female spouses. In the majority of the twin families both the twins and their parents were born in the Netherlands (see Table 2a). The other families come from all over the globe (e.g., Surinam, the Netherlands Antilles, Morocco, Turkey, Indonesia, West and Eastern Europe, North America and Asia).

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Address for correspondence: Dorret Boomsma, Department of Biological Psychology, Vrije Universiteit, Van der Boechorststraat 1, 1081 BT, Amsterdam, the Netherlands. E-mail: dorret@psy.vu.nl

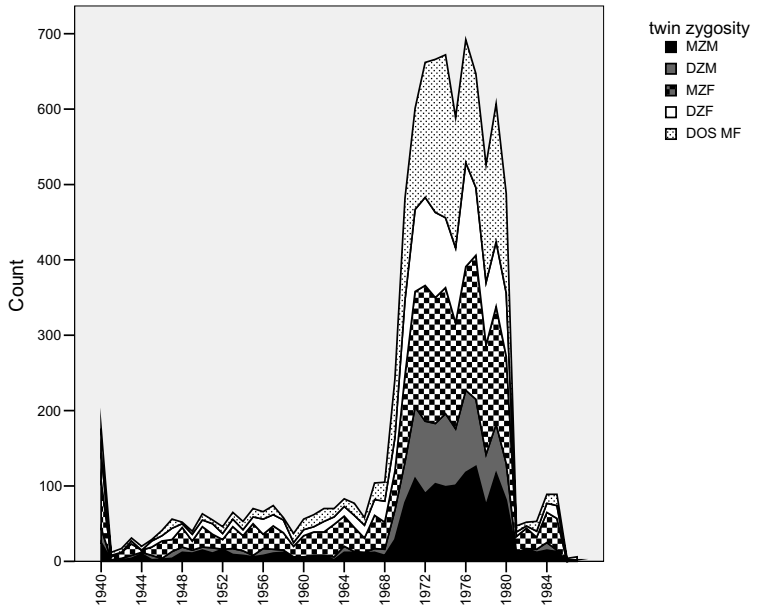

Figure 1

Number of twins (cumulative distribution) in the ANTR as a function of zygosity, per birth cohort (1940–1987). Date of birth of twins born before 1940 was recoded as 1940.

Table 1

ANTR: Adults Registered with the Netherlands Twin Register Who Participated at Least Once in Survey and/or Laboratory Studies

Family relation	Number
Twin	
MZM	1566
DZM	1136
MZF	2875
DZF	1647
DOS	2354
Zygosity unknown	255
Triplet and other multiples	66
Siblings of twins	
Brother	1412
Sister	1767
Sex unknown	71
Parents of twins	
Father	2999
Mother	3373
Spouses of twins	
Male	1223
Female	674
Sex unknown	61
Offspring of twins	
Male	81
Female	144
Offspring of siblings	
Male	22
Female	59

A total of 7 surveys have been sent out to the adolescent and adult twins. The seventh survey was mailed out in 2004/2005 to all twins and their family members. Participants in special projects, or subjects whose new address had recently been recovered, are still approached with the request to complete this survey. As a pilot project, we approached a small group of adult (i.e., 18 years or older) offspring of twins and siblings. For the first time, Dutch-speaking twin families in Belgium were also asked to take part in the study. The seventh survey was mailed to Belgian twin families and a total of 1859 twins and their parents returned the questionnaires.

All surveys include assessments of lifestyle variables (drinking, smoking and exercise behavior), health information (e.g., body mass index, migraine, subjective health), demographic characteristics (e.g., education, religion) and personality and psychopathology (e.g., sensation seeking, depression). Table 3 offers an overview of the longitudinal data structure of surveys 1 through 7. As can be seen, most participants returned more than one survey (please note that only twins could participate in all seven surveys).

YNTR

The young twins are registered at birth by their parents. During the first years of their lives the parents are the primary sources of information on their development. Parents complete surveys about the twins' behavior and development at ages 0, 2, 3, 5, 7, 10 and 12 years. In addition, parents are asked for permission to approach the teachers of the twins

Table 2a

Number of Twins Registered with ANTR by the Country of Own and Parental Origin and Zygosity

	Total	MZM	DZM	MZF	DZF	DOS	Twin*
Twins and both parents born in NL	8164	1306	978	2388	1407	2037	48
Twins born in NL, one parent abroad	309	43	37	97	57	73	2
Twins born in NL, both parents abroad	128	20	8	44	19	34	3
Twins and both parents born abroad	77	11	8	28	14	16	0
Twins and one parent born abroad	30	4	2	11	6	7	0
Twins born abroad, both parents NL	62	10	8	20	8	15	1
Information missing for birth country	1063	172	95	287	136	172	201
Total	9833	1566	1136	2875	1647	2354	255

Table 2b

Number of Twins Registered with YNTR by the Country of Own and Parental Origin and Zygosity

	Total	MZM	DZM	MZF	DZF	DOS	Twin*
Twins and both parents born in NL	18,365	2343	3436	2682	3136	6337	431
Twins born in NL, one parent abroad	1292	164	277	185	221	406	39
Twins born in NL, both parents abroad	332	43	69	54	46	97	23
Twins and both parents born abroad	12	4	2	2	2	1	1
Twins and one parent born abroad	22	2	6	5	3	5	1
Twins born abroad and both parents NL	61	6	8	11	10	25	1
Information missing for birth country	552	70	106	61	97	198	20
Data not entered yet	5258	33	9	36	11	1727	3442
Total	25,894	2665	3913	3036	3526	8796	3958

Note: *Zygosity unknown.

at ages 7, 10 and 12 years. At ages 0 and 2 data collection focuses on events surrounding pregnancy and birth, health, growth and attainment of milestones. From age 3 years onwards, information on the twins is collected from both parents and is targeted at the development of emotional and behavioral problems, as assessed by the Child Behavior Checklist (CBCL). Teachers complete the Teacher Rating Forms (TRF). The CBCL and TRF assess very similar constructs (Achenbach, 1991). Comparisons of CBCL data from twins to data from epidemiological studies in singletons have shown that twins are comparable to singletons at age 3 (Van den Oord et al., 1995) as well as at later ages (unpublished results).

The total number of families with young twins who take part is 25,894. The twins are MZ in 5701 (22%) families, same-sex DZ in 7349 (29%) families, opposite-sex twins in 8796 (34%) families, and of unknown zygosity in 3958 (15%) families. This last group of families consists of families with newborn twins or twins below the age of 5 years (zygosity based on questionnaire data is usually not assigned before the survey at age 5 years has been collected and the data entered into the database;

Table 3

Number of Times Subjects Participated in ANTR Surveys Between 1991 and 2005

	1	2	3	4	5	6	7	Total
Twin/Triplet	2836	1917	1832	1094	895	707	379	9660
Sibling	1078	763	526	463	263	0	0	3093
Parent	1926	1510	1019	951	719	1	0	6126
Spouse	927	839	191	0	0	0	0	1957
Offspring	309	0	0	0	0	0	0	309
Total	7076	5029	3568	2508	1877	708	379	21,145

Note: The maximum number of times twins could participate was 7, for parents 5 (not in 1997 and 2000), for siblings 5 (not in 1991 and 1993), for spouses 3 (from 2000 onwards; in 2000 only a limited number of spouses were invited to take part in the survey study), and for offspring of twins once (in 2004/5).

Table 4a

Overview of Experimental and Laboratory Studies of ANTR

	N			Age of twins	DNA sampling		
Study	Parents	Twins	Siblings		Twins	Siblings	Parents
Cardiovascular adolescent[1]	320	320	—	14–21	Yes	—	Yes
Cardiovascular adult[2]	—	426	—	34–63	Yes	—	Part
Cardiovascular ambulatory[3]	—	553	263	15–76	Yes	Yes	Yes
Depression (CIDI)[4]	266	430	318	14–77	Yes	Yes	Yes
EEG/ Cognition adolescent*[5]	—	426	—	16–18	Part	—	—
EEG / Cognition adults[6]	—	566	194	18–71	Part	Part	—
MRI adults[7]	—	224	34	19–68	Part	Part	—
fMRI depression [8]	—	64	—	18–50	Yes	—	—

Note: [1]Boomsma et al. (1996); [2]Snieder et al. (1997); [3]Kupper et al. (2005); [4]Middeldorp et al. (2006); [5]Van Beijsterveldt et al. (2001); [6]Posthuma et al. (2005); [7]Baare et al. (2001); [8]De Geus et al. (in press).

*Longitudinal studies (the number of twins indicates the number at first measurement).

Table 4b

Overview of Experimental and Laboratory Studies of YNTR

	N			Age of twins*	DNA sampling		
Study	Cohort	Twins	Siblings		Twins	Siblings	Parents
EEG / Cognition, children[1]**	1986–88	418	—	5, 7, 10, 12, 18 years	Yes	—	Yes
ADHD clinical study[2]	1989–94	1006	—	10–13 years	Yes	—	Yes
MRI-ADHD[3]	1986–92	50	—	15 years	Yes	—	Yes
Attention & IQ*[4]	1990–92	474	55	5 and 12 years	Yes	Yes	—
MRI /cognition*[5]	1995–96	224	103	9 and 11 years	Yes	Yes	Yes
Motor milestones*[6]	2003–04	470	—	6–18 months	Yes	—	Yes

Note: [1]Bartels et al. (2002); [2]Derks et al. (2006); [3]Van 't Ent et al. (2005); [4]Polderman et al. (2006); [5]Van Leeuwen et al. (2006); [6]Brouwer et al. (2006).

*Longitudinal studies (the number of twins indicates the number at first measurement).

**in progress.

although questions about zygosity are also asked at earlier ages). Table 2b gives a summary of the number of twin pairs in the YNTR born abroad and in the Netherlands. For the birth cohorts 1987 to 1998, Figure 2 gives the breakdown of zygosity by birth cohort. As can be expected, the number of DZ twins who are registered is increasingly larger than the number of MZ twins, which reflects the general trend in the Netherlands that relatively more DZ than MZ twins are born, because of increasing maternal age and assisted reproduction.

In subsamples of twins and siblings aged 11 and 12 years we have collected self-report data using the Youth Self-Report (YSR; Achenbach, 1991) on behavioral and emotional problems. These twins and siblings take part in substudies of cognition, ADHD, or brain imaging. A total 1146 twins and 44 of their siblings who enrolled in these studies have returned a self-report survey. At ages 14, 16 and 18 all young twins receive a self-report survey by mail. At this time their siblings are also approached. This survey again assesses behavioral and emotional problems, as well as lifestyle variables (smoking, drinking and exercise behavior), growth, health, well-being and academic performance. The surveys are sent to the parents, and twins and siblings are asked to complete these surveys once their parents have given permission. Currently 2249 twins and 423 siblings have participated in this new survey project.

Experimental and laboratory studies and special projects

The ANTR and YNTR databases are used to invite twin families to take part in phenotyping studies of, for example, cardiovascular risk factors, cognition, attention problems and development of brain structure. An overview of experimental and laboratory studies is given in Tables 4a and 4b. Several projects invited random samples from the NTR to the laboratory in order to study the genetics of cognition and brain function and structure in children (Bartels et al., 2002; Polderman et al., 2006, van Leeuwen et al., 2006) and in adults (Van Beijsterveldt et al., 2001; Posthuma et al., 2005), or to assess cardiovascular risk factors (Boomsma et al., 1996, Snieder et

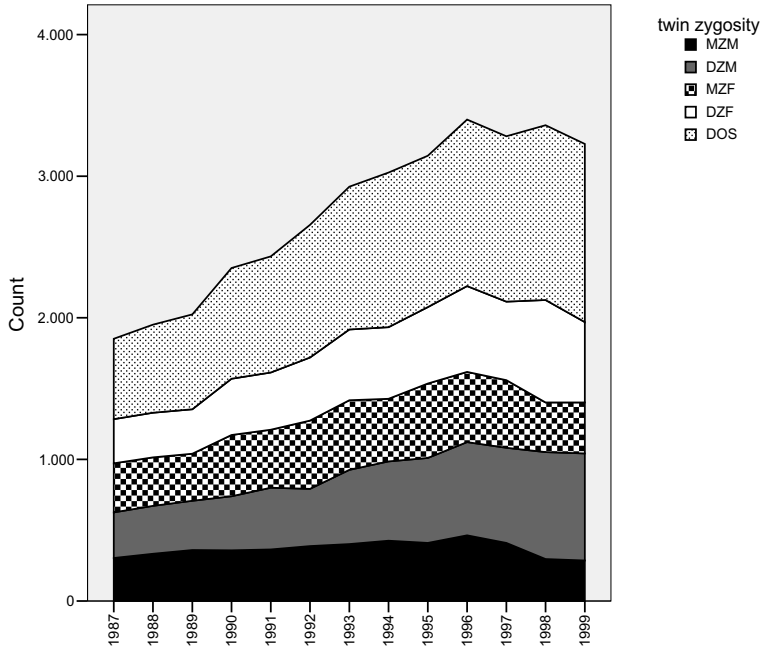

Figure 2

Number of twins (cumulative distribution) in the YNTR as a function of zygosity, per birth cohort (1987–1999). Data of twins born after 1999 were omitted, because zygosity is usually assigned at age 5 years.

al., 1997). For a linkage project on anxiety and depression (Boomsma et al., 2000) we selected high and low scoring siblings and asked them and their family members for a DNA sample. Offspring were asked to participate in a psychiatric interview (Middeldorp et al., 2006) and were visited at home (Kupper et al., 2005) for 24-hour ambulatory assessment of blood pressure, impedance cardiography, respiration rate and heart rate. Finally, special groups such as MZ pairs discordant for depression or for attention problems take part in structural and functional MRI studies to examine environmental pathways into these disorders (De Geus et al., in press; Van 't Ent et al., 2005).

Spontaneous DZ twinning in humans is under genetic control. In collaboration with the Australian Twin register (Montgomery et al., 2003, 2004), phenotype and genotype information are collected for linkage and association studies in sisters who are both mothers of DZ twins. As a first step, we sequenced the GDF9 (GDF9 in sheep causes increased ovulation rate) coding region in DNA samples from 20 women with DZ twins and identified a four-base pair deletion in GDF9 in two sisters with twins from one family.

We initially started DNA collection in the groups that are shown in Table 4 by collecting buccal swabs. A large number of these DNA samples from families informative for linkage (a family consisting of at least 1 sibling pair) have been genotyped. Genotyping for the two cardiovascular studies was done by the Molecular Epidemiology Section, Leiden University Medical Centre, the Netherlands (Heijmans et al., 2005). All other genotyping was carried out by the Mammalian Genotyping Service, Marshfield, United States, in two separate batches.

Table 5

Number of Families With More Than One Set of Multiples (No Selection on Phenotype Information)

Family with	YNTR	ANTR	YNTR and ANTR	*N* families
Two twin pairs	193	52	23	268
Twin and triplet	7	0	0	7
Three twin pairs	3	1	1	5
Triplets	533	49	—	582
Quadruplets	6	3	—	9
Quintuplets	2	—	—	2

NTR Biobank

Currently, all ANTR subjects over 18 years old are invited to take part in the NTR-Biobank project. Subjects are invited by letter, which is followed by a telephone call and a home visit if the twin or their family members agree to take part. Home visits take place between 7 and 10 am, following fasting by subjects since the previous evening. Fertile women are bled on 2 to 4th day of the menstrual cycle, and women taking oral contraceptives in the pill-free week (Hoekstra et al., 2004). Over 6000 samples have been

collected. When the home visit takes place, six tubes of blood (EDTA, heparin, serum, citrate) and two small tubes of urine are collected. RNA samples are collected in challenged and unchallenged whole blood samples (Spijker et al., 2004). A few traits (e.g., lipids, CRP, insulin, glucose, white blood cell count, HbA1c) are assessed immediately in fresh blood samples, and the rest of the material is frozen for later processing.

Special family relations

There are several special groups of participants in the NTR. As a first example, in the ANTR there are 263 twins (69 males and 194 females) who are also parents of twins (two of those are parents of two sets of twins). There is one adult pair in which both twins are mothers of twins. In some of these families the parents of these twins (63 mothers and 52 fathers) are also registered with the NTR. In the YNTR (which registers twins at birth and asks parents for ratings of their children) there are 533 mothers and 528 fathers who themselves are twins and 17 couples in which both parents of young twins are a twin themselves.

As a second example, there are 303 families with more than one sibling who is the parent of twins. In these 303 families there are a total of 762 siblings (680 women) who are parents of twins. In these families we have registered 370 parents of the sibling sets with twins (165 fathers and 205 mothers). Finally, there are a large number of families with triplets or other higher order multiples and with more than one set of twins or triplets (see Table 5).

Discussion

The NTR has gone beyond the traditional twin design by including family relationships other than MZ and DZ twins in the register. This has made a restructuring of the database an obvious necessity. It is relatively straightforward to specify biological relations among participants. It is much more complicated to also specify dynamic, social relationships and to keep track of the history of these family relations. For example, parents of young twins may divorce, and remarry so that both biological and nonbiological parents provide ratings of twins' behavior. Young twins are also rated by their teachers, and these relations are now also stored. In the ANTR, spouses of twins are asked to participate. In 2000, spouses of twins aged between 25 and 30 years were invited, and in 2002 and 2004, all spouses of twins received an invitation. Because the ANTR twins are on average still young, there are a lot of changes in spousal relationships and there are a substantial number of twins whose first and second spouse (defined as current partner/significant other) are both in the database.

The large number of surveys which has been collected in the YNTR and ANTR has made it possible to use the item database for the construction of new scales to assess aspects of personality and psychopathology. We used the CBCL data from young twins and the YSR data from adults to construct a scale that assesses obsessive-compulsive symptoms (OCS). Genetic analyses of these scales showed significant heritabilities both in children and adults for this phenotype (Hudziak et al., 2004; Van Grootheest et al., in press)

The CBCL data from 7-, 10- and 12-year-old twins were also used to look at juvenile bipolar disorder which was defined as the sum score of Attention Problems, Aggression and Anxious/Depressed behavior. Heritability of the CBCL-juvenile bipolar disorder (CBCL-JBD) increases with age (from 63% to 75%) whereas the effects of shared environment decrease with age (from 20% to 8%). The stability of the CBCL-JBD phenotype is high (Boomsma et al., 2006b). Genetic factors account for the majority of the stability.

In adults, we are currently examining the heritability of Type D behavior (Denollet et al., 2006) which is defined as a combination of social inhibition and neuroticism and could be reliably reconstructed using items from the CBCL withdrawn scale and the ABV neuroticism scale (Wilde, 1970). Items from the YSR inventory have also been used to look at the genetic contributions to variation in loneliness (Boomsma et al., 2005, 2006a).

Using robust maximum likelihood (MLR) estimation which corrects for the dependency of traits within families (Rebollo et al., 2006), the database can also be used to carry out factor analyses of tests and items, and to explore associations among variables. For instance, we showed that exercise behavior was associated with lower levels of neuroticism and higher levels of sensation seeking and extraversion (de Moor et al., 2006). Also, large cross-sectional data sets can be obtained by combining data from different measurement occasions. As an example we selected for all participants the first survey they returned to examine the heritability of exercise behavior. A large dataset was created that showed substantial changes in genetic architecture over age. Up until the age of 15 years, variance in exercise behavior was mainly due to common environmental factors whereas it became almost entirely genetic at around age 20 (Stubbe et al., 2005).

To test some of the assumptions underlying the twin method, data from twins can be modeled simultaneously with data from their siblings. To carry out such an analysis on data on sensation seeking, twins and their nontwin siblings were selected from the longitudinal dataset. The data for the siblings was taken from a survey in which they were measured at about the same age as the twins. Compared to the twins, we selected an earlier survey of older siblings and a later survey for younger twins (Stoel et al., 2006). In addition to a comparison of the phenotypic resemblance between MZ and DZ twins, this design allows for an explicit test of the assumption that results from twins may be generalized to the singleton population. Second, it offers the opportunity to investigate to what extent the influence of common environment is the

same for twins and siblings, that is, allows for explicit tests of a special twin environment.

A large database of well-phenotyped twins and family members makes new, quasi-experimental, designs possible. The MZ discordant (MZD) design is a powerful method to look at environmental pathways that mediate differences within MZ pairs. We have carried out a MZD study of depression in adults (de Geus et al., in press) and of attention problems in adolescent twins (Van 't Ent et al., 2005), using (f)MRI. A new fMRI study of obsessive-compulsive disorder in MZ discordant pairs is currently in progress.

An exciting new development is the possibility of linking the NTR data to other databases in the Netherlands. We have included a question in the 6th and 7th surveys to adults asking for permission to link data. Also, all mothers of young twins received a questionnaire about familial twinning in 2005 which included one question requesting permission to link data. The majority of participants has no objection. In ANTR survey 6, 87% of all participants gave permission, whereas only 9.1% said no and 3.9% did not reply. In survey 7, 91.3% said yes, 5.7% replied no and 3% did not answer the question.

In conclusion, the NTR combines the classical twin design with extended and more complex family designs to genetic epidemiology and heritability studies. The combination of longitudinal phenotyping with large-scale DNA typing hopefully will elucidate the underlying genetic mechanisms that cause variation in a wide range of health, physical, behavioral and psychological characteristics.

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